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January 10, 2005

Dockets Management Branch
Food and Drug Administration
Department of Health and Human Services
Room 1061, HFA-305
5630 Fishers Lane
Rockville, Maryland 20852

RE: ANDA Suitability Petition 2004P-0085 / CP2
Esmolol Hydrochloride for Injection

We are submitting comments to this petition in response to a May 28, 2004 (2004P-0085 CP 1) submission made by Baxter Healthcare Corporation to this petition.

Baxter states that the original petition should be denied based on several points made throughout the petition. The following comments correspond to the points made in the comments provided by Baxter labeled using Roman numerals.

I. Stability claims

The information provided in the original petition was for the total impurity content and not for the major degradant only. Although detailed full shelf life information is not provided in the petition, early indications on pilot studies suggest that the lyophilized form will yield a lower total impurity level at the expiration. Full stability information and impurity evaluation would be a requirement for the ANDA review process. The proposed lyophilized product would have to provide a product with at least the same, if not improved, impurity profile in relation to Brevibloc®.

In addition, Baxter suggests that impurity ASL-8123 could act as a heat sink in the lyophilized product upon reconstitution and could accelerate the degradation of esmolol. The current Brevibloc is already in a liquid form and provides a level of impurity that is significantly higher than that of the lyophilized form. The theory of a heat sink and increased degradation is merely conjecture on the part of Baxter as they have not provided any analytical data with their comments.

II. Medication Errors

It is our opinion that a lyophilized Esmolol product will not create additional medication errors because it differentiates itself from the liquid versions. The currently marketed liquid products are the same fill size with the only difference being a 25 fold increase in concentration A lyophilized form will necessarily create an obvious difference between the strengths.

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Although the reconstitution concentration (100 mg/mL) of the lyophilized product is different than the current concentration (250 mg/mL) of the Brevibloc product, it still requires the transfer of the entire contents of the vial, just as the current Brevibloc requires transfer of the complete contents. Therefore, after the reconstitution step, the preparation steps are virtually the same for both products.

Hospital staff and pharmacists are familiar with reconstituting lyophilized products as there are multiple other products in the market that are provided in a lyophilized form. Therefore, Baxter's comments concerning an increased risk of contamination because of the reconstitution step is no more likely than the risks associated with other lyophilized products.

It is our opinion that a lyophilized dosage form creates enough of a difference to prevent medication errors between the 2.5 g/10 mL and 100 mg/10 mL dosages simply because of the visual difference which would be immediately observed. The current dosages of Brevibloc are both liquids and are the same fill size and can lead to errors due to haste or carelessness. Although the proposed form does require an additional reconstitution step, this is a step commonly performed with any lyophilized product. It would be particularly notable because the product could not be transferred to the IV bag without its completion, forcing the preparer to consult the package insert.

Baxter goes on to state that significant labeling changes would be necessary to address safety or effectiveness problems. The use of a lyophilized form does not create efficacy problems and we believe that the safety risks due to medication errors are no greater than those already currently presented by Brevibloc. The labeling includes the revised reconstitution and preparation instructions for the lyophilized product. These changes don't constitute significant changes in labeling and were provided in the original petition.

Lastly, there are comments regarding the homogeneity and incomplete mixing of a lyophilized product. This again, would be a common theme in all lyophilized products. In addition, the entire contents of the vial are withdrawn and added to an IV bag, therefore, the entire dose will be delivered. The lyophilized product is reconstituted with water and added to a water base IV bag. The Reference Listed Product contains organic components which, one could theorize, may provide more of a mixing challenge when added to the IV bag, than would be encountered with the water based lyophilized product.

In addition, it is not unusual to have both a liquid and lyophilized dosage form of a product. There are a number of products which are available in both lyophilized and liquid form, such as Doxorubicin, Daunorubicin, Cisplatin, Carboplatin, and Leucovorin Calcium. The only difference in lyophilized and liquid labeling for these products is to provide for reconstitution instructions. Methotrexate is also provided in both a liquid and a lyophilized form with the lyophilized product being reconstituted to a different

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concentration than the liquid form. The lyophilized form can be reconstituted to 50 mg/mL, while the liquid form is 25 mg/mL.

III. Providing a cheaper alternative that doesn't infringe patent rights.

We acknowledge Baxter's comments concerning patent infringement and agree that is a subject for ANDA certifications. Bedford is well aware of the patents for Brevibloc as we are currently marketing the 100 mg/mL dosage form based on the approval of a Paragraph IV ANDA.

Sincerely,

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